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A RANDOMIZED COMPARISON OF TAMOXIFEN VS. CMF USING CREATININE CLEARANCE FOR DOSE MODIFICATION IN ELDERLY BREAST CANCER PATIENTS. AN ECOG STUDY. SG Taylor IV[1], R Gelman, F Cumming, G Falkson for the Eastern Cooperative Oncology Group. [1]Rush Medical College, Chicago, IL.

194 pts. over age 65 having metastatic breast cancer entered a randomized trial of tamoxifen (T) 20 mg. daily vs. cyclophosphamide (C), methotrexate (M), and 5-fluorouracil (F). Dosage of F was 400 mg/m^2 on d 1 and 8. Creatinine clearance (Cr cl) determined dosage of C as 100 mg x Cr cl/70, orally daily, d 1-14, and M as 40 mg x Cr cl/70, intravenously D 1 and 8, not to exceed 100 mg/m^2 or 40 mg/m^2 respectively. Cycles were repeated every 28 d. Hematologic toxicity and mucositis guided subsequent CMF dosage. Upon progression, patients received the alternative regimen. A withdrawal period to assess withdrawal response followed cessation of T. Thirty-seven percent of 85 eligible pts responded to CMF vs. 44% of 96 pts to T on step 1 (p=.37). Thirty-one percent of 45 pts. and 29% of 49 pts. responded to CMF or T respectively on crossover. Only 3 of 82 pts. (4%) had T withdrawal response but an additional 29 (35%) of these had stable disease for .7 mo. (median 2.6, range 2 - 7.1 mo.). Median time to failure and survival of all pts.was 6.1 mo. vs. 6.1 mo. and 20.1 vs. 24.1 mo. respectively for pts. given CMF or T on step 1. Duration of response to the two regimens was 9.4 and 9.9 mo respectively. Response by ER status for CMF was 52% for ER+, 43% for ER-, 23% ER unknown. For T the values were 49%, 23% and 46% respectively. Dose modification of CM based on Cr cl resulted in no increased hematologic or mucous membrane toxicity from CMF in older pts or in those with compromised Cr cl. We conclude both CMF and T are effective therapies for elderly pts. with advanced breast ca independent of sequence of treatment. Combination chemotherapy can be safely administered to this elderly population provided altered Cr cl is considered. Hormone therapy may be worthwhile even in ER- pts. in this elderly population. Hormone withdrawal may extend disease control in a considerable minority of pts. prior to institution of other therapy.

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PRELIMINARY OBSERVATIONS OF THE CARDIOTOXICITY OF 4'-EPI-DOXORUBICIN: EVALUATION BY ENDOMYOCARDIAL BIOPSY. FM Torti, MR Bristow, AE Howes, D Aston, M Kohler, EP Mitchell, ME Billingham. Divisions of Medical Oncology; Cardiology & Pathology, Stanford University Medical Center; Palo Alto VA Medical Center; and the Northern California Oncology Group (NCOG), Palo Alto, CA 94304.

Forty-six endomyocardial biopsies have thus far been performed in 30 patients receiving 4'-epi-doxorubicin (4EPI) (Epirubicin, Farmitalia) in doses ranging from 147 to 868 mg/m^2. These patients are part of phase II studies of 4EPI in colorectal, melanoma, breast, and lung cancer in the NCOG. Cardiac damage was evaluated by a scoring system previously described (Cancer 50:32. 1982).

The degree of endomyocardial damage of 4EPI was compared to 119 endomyocardial biopsies in patients receiving doxorubicin every 3 weeks and 41 biopsies in patients receiving doxorubicin weekly. Multivariate analyses were performed with dose, prior cardiac irradiation, and regimen (4EPI vs 3-weekly and weekly doxorubicin). If equal potency of doxorubicin and 4EPI are assumed, then 4EPI is less cardiotoxic than 3-weekly doxorubicin, and borderline less cardiotoxic than weekly doxorubicin.

Regimen	p
3-weekly doxorubicin vs 4EPI	P = .0005
Weekly doxorubicin vs 4EPI	P = .06

Since variable potency of analogs is a general problem in comparing efficacy and toxicity of analogs with parent compounds, a general model has been devised which allows comparison of endomyocardial biopsy scores, given variable potency of evaluated drugs. Although the relative potency of 4EPI and doxorubicin is still undergoing clinical evaluation, preliminary analysis suggests 4EPI remains less cardiotoxic than 3-weekly doxorubicin even if a relative potency of 0.8:1.0 for 4EPI to doxorubicin is assumed (p=.05).

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PHASE I STUDY OF HOMOHARRINGTONINE (HHT) IN 10 DAY SCHEDULE: 6 HR INFUSION DAILY VS CONTINUOUS INFUSION. Stephen C. Malamud, Takao Ohnuma, Valerie Coffey, Paulo Alberto Paciucci, Louis R. Wasserman and James F. Holland. Departments of Neoplastic Diseases and Medicine, Mount Sinai School of Medicine, New York, NY 10029.

HHT is one of the alkaloids isolated from Cephalotaxus fortunei. It inhibits the initiation of protein synthesis. Clinical studies in China revealed that HHT is active against leukemia and lymphoma. In 29 pts (27 with solid tumor, 1 lymphoma and 1 AML; 16M: 13F; median age 54, median PS 2-5, 26 pts had prior chemotherapy with a median of 5 agents, 22 pts had prior radiotherapy), we gave 36 evaluable courses. Two schedules were tested; (a) 6 hr infusion daily x 10 (n=22) and (b) continuous infusion x 10 days (n=14). In (a) the dose was escalated from 0.5 to 6.0 mg/m^2/d. At ≥2.0 mg/m^2/d, 5 of 14 courses were interrupted because of hypotension, tachycardia and/or arrhythmia but only once due to leukopenia. In (b) only 2 of 14 courses were interrupted due to cardiovascular complications (CVC); 3 were interrupted because of progressive leukopenia and/or thrombocytopenia. CVC were seen in 14/22 in (a) but only 4/14 in (b). In (a) the median WBC and PLT (x10^3/ul) fell to 3.6 and 53 at 2.0 mg/m^2/d, and 1.6 and 29 at 4.0 mg/m^2/d, respectively. In (b) they were 4.2 and 53 at 2.0 mg/m^2/d, 6.8 and 165 at 3.0 mg/m^2/d, 0.5 and 24 at 4.0 mg/m^2/d, 0.18 and 12 at 6.0 mg/m^2/d. Other toxicities were N&V 7, mucositis 3, diarrhea 3, depression-lethargy 10, agitation-confusion 2, transient elevation of GOT/GPT 5, creatinine elevation 3 and hyperglycemia 2. There were no CR or PR. Schedule modification from a 6 hr to a 24 hr infusion resulted in reduction in the incidence of CVC with comparable marrow toxicity. 4.0 mg/m^2/24 hr x 10 is the MTD for patients with solid tumors. 5.0-6.0 mg/m^2/24 hr x 10 is currently being tested in patients with leukemia.

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CARBOPLATIN: ACTIVITY IN PATIENTS WITH HEAD AND NECK (H&N), RENAL CELL (RC) AND OVARIAN CARCINOMAS. Takao Ohnuma, Serge Leyvraz, Valerie Coffey, Hugh Biller, Franco Muggia and James F. Holland. Depts of Neoplastic Diseases and Otolaryngology, Mt. Sinai School of Medicine, New York, NY 10029 and Cancer Center, New York University School of Medicine, New York, NY 10016.

Carboplatin (diammine 1,1-cyclobutanedicarboxylato-(2-)-O,O' platinum; CBDCA) is a second generation platinum coordination complex. 23 pts, 14M/9F, medians 61 yrs, performance status 1, with squamous cell Ca of the H&N, RC Ca and ovarian Ca received carboplatin at a dose of 500 mg/m^2 bolus q 4-6 w (previously untreated) or 270-400 mg/m^2 bolus (previously treated). Prior cisplatin exposure was 1/13 with H&N, 0/6 RC and 4/4 ovarian Ca. Of 13 pts with H&N Ca there were 2 PR (20+,8+ wks), 1 MR (15+ wks) and 3 SD (16, 8+,4+ wks). Of 6 pts with RC Ca there were 1 PR (8 wks) and 4 SD (28+, 12+, 8+, 4+ weeks). Of 4 pts with ovarian Ca there were 1 PR (17+ wks) and 1 MR (16 wks). N&V were well controlled with prochlorperazine and/or metoclopramide. The major toxicity was myelosuppression. In previously untreated pts 500 mg/m^2 i.v. bolus produced a median WBC nadir (x 10^3/ul) of 3.0 (range 1.0-8.5, median day 12) and PLT (x10^3/ul) 55 (range 7-329, day 18). Subsequent dosing of 500 mg/m^2 was not cumulative with a median WBC nadir of 2.7 (day 16) and PLT 63 (day 15). Carboplatin was less well tolerated in previously treated ovarian cancer pts (3/4 with 3rd space fluid). Thus, after 270 mg/m^2 median WBC and PLT nadirs were 3.0 (day 22) and 40 (day 21), respectively. Fall in Hgb was cumulative with repeated dosing: all of 7 pts receiving more than 3 cycles of the drug required RBC transfusions. There were no renal, oto- or neurotoxicities. Carboplatin appears to be active in the treatment of H&N, RC and ovarian carcinomas. Response seen in pts with prior exposure to cisplatin is noteworthy.

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Homoharringtonine: a phase I evaluation

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Summary

Homoharringtonine is one of several Cephalotaxine esters which have shown experimental antineoplastic activity as well as anti-leukemia effects in patients in China. In a Phase I trial of homoharringtonine administered daily × 5 by bolus intravenous injection, the dose limiting toxicity was hypotension and the maximum tolerated dose was 3.5 mg/m²/d × 5. Evidence of drug induced cardiac irritability with resulting ventricular and atrial dysrhythmias was seen. Minimal myelosuppression was seen at this dose. Treatment of patients by 5 day continuous intravenous (rather than bolus) infusion resulted in more pronounced myelosuppression and clinically significant but tolerable hypotension. Significant reduction of white blood cell and platelet counts occurred at a dose of 3.5 mg/m²/day. Further investigations of the hypotensive and cardiac effects of homoharringtonine and Phase II trials using continuous infusion are indicated.

Introduction

The use of natural plant products in the treatment of disease has for centuries been an important component of medical therapy. Recently the *Cephalotaxus* genus of coniferous trees and shrubs has been exploited as a source of antineoplastic agents (1). The alkaloids harringtonine and homoharringtonine have been used as anti-leukemic agents in China (2, 3) and homoharringtonine (Figure 1) is currently being evaluated in the United States. While the prototype alkaloid Cephalotaxine is itself inactive against experimental tumors, the esters harringtonine, iso-harringtonine, homoharringtonine, and deoxyharringtonine demonstrate various degrees of activity against P388 and L1210 leukemia (4). Harringtonine and homoharringtonine (HH) are the most promising agents as judged by preclinical antitumor testing, and the greater yield of HH from the plant has led to the choice of this compound for clinical evaluation (5).

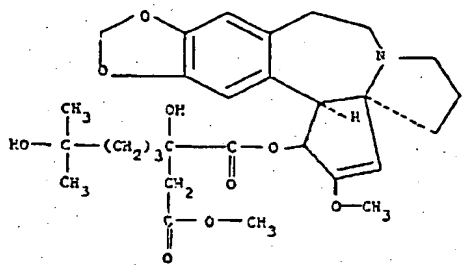

Fig. 1. Homoharringtonine, NSC 141633. Chemical name: Cephalotaxine, 4-methyl-2-hydroxy-2-(4-hydroxy-4-methylpentyl) butanedioate ester.

Though much of the biochemical evaluation of this class of compounds has been done with harringtonine, the principal effects of HH, which has an additional methyl group in the side chain, have been similar (5). Studies in HeLa cells demonstrate that harringtonine inhibits the initiation of protein

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synthesis as well as DNA synthesis as a presumed secondary phenomenon (6). These effects are partially reversible in a dose and time dependent manner.

The antitumor activity of HH in experimental systems is dependent upon treatment schedule. HH is active against a number of murine tumors including the B16 melanoma, the $CD8F_1$ mammary carcinoma, the L1210 leukemia, and is especially active against the colon 38 tumor and P388 leukemia. In the i.p. implanted P388 system, single intravenous dose therapy was ineffective, but antitumor activity increased as the frequency of administration increased. Daily intravenous treatments produced an ILS of 100% (5).

Preclinical toxicological studies included the evaluation of the effects of HH in beagle dogs. Myelosuppression, particularly leukopenia, was the most commonly observed toxicity. Other effects included emesis, diarrhea, and cardiac dysrhythmias that were seen at all dose levels in the daily times five schedule (5). Toxicologic studies reported in the Chinese literature suggested that the cardiac effects were dose related and reversible upon discontinuation of treatment (2).

Homoharringtonine has been used for treatment of leukemia in China since 1974 with reported therapeutic effect (2, 3). Many of the Chinese patients were treated with mixtures of harringtonine and homoharringtonine, using a wide variety of doses and treatment schedules. The greatest benefit was seen in those patients with acute myelogenous leukemia. The Chinese reports of anti-leukemic effect and the promising preclinical antitumor activity seen in murine systems have stimulated clinical evaluation of HH in this country. We have evaluated HH in a Phase I clinical trial using a daily times five schedule with both bolus administration and continuous infusion of the drug. The purpose of this trial was to establish tolerable doses for future Phase II trials and to evaluate and describe the toxicity seen in humans when treated with this agent.

Patients and methods

The initial trial conducted at the Vermont Regional Cancer Center, University of Vermont, was with HH given as a bolus on a daily times five schedule. Following this Phase I trial with bolus administration, additional patients were treated with HH using a daily times five continuous infusion schedule. Data from each of these studies are presented separately.

Patients were eligible for treatment with HH if they had pathologically proven cancer that was resistant to conventional treatment or for which there was no standard treatment with a reasonable expectation of benefit. Informed consent consistent with Federal and University of Vermont guidelines was obtained from each patient prior to entry in the study.

HH was supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland. The initial supplies of drug required reconstitution with dehydrated alcohol followed by dilution with saline, which yielded a solution of HH 1 mg/ml in 10% ethanol. In January of 1983, the drug formulation was changed to a lyophilized powder requiring only reconstitution with saline to yield a solution containing 2 mg of HH per ml.

Bolus administration

Seventeen patients were treated with 32 courses of HH (Table 1). The daily dose of drug was dissolved in 100 ml of 5% dextrose in saline and given by intravenous injection over 10 minutes. The planned schedule treatment was for five consecutive days of treatment followed by at least two weeks of observation prior to a second course of drug at the same or higher dose level. The initial daily dose used was 1/30 of the LD_{10} in the mouse or 0.2 mg/m²/day. This particularly low starting dose was chosen because of concern for potential cardiovascular toxicity. Patients with congestive heart failure or a history of significant cardiac dysrhythmias were excluded from this trial.

Prior to therapy, patients underwent evaluation which included physical examination, history, com-

Table 1. Patient characteristics – Bolus HH

Characteristics	Number of patients
Total	17
Male	6
Female	11
Median age in years (range)	
Male 55 (32–72)	
Female 58 (36–70)	
Prior therapy	
None	3
Chemotherapy alone	7
Radiotherapy alone	2
Chemotherapy & Radistion therapy	5
Tumor types	
Colorectal carcinoma	7
Testicular carcinoma	1
Ovarian carcinoma	2
Breast carcinoma	1
Non small cell lung carcinoma	4
Renal cell carcinoma	1
Adenocarcinoma, unknown primary	1

Table 2. Patient characteristics – Continuous infusion HH

Characteristics	Number of patients
Total	12
Male	8
Female	4
Median age in years (range)	
Male 65 (58–70)	
Female 58 (52–67)	
Prior therapy	
None	1
Chemotherapy alone	4
Radiotherapy alone	2
Chemotherapy & Radiation therapy	5
Tumor types	
Adenocarcinoma, esophagus	1
Adenocarcinoma, unknown primary	1
Colorectal carcinoma	3
Squamous cell carcinoma, mouth	1
Non small cell lung carcinoma	3
Multiple myeloma	1
Diffuse histiocytic lymphoma	1
Adenocarcinoma, pancreas	1

plete blood count and chemistry tests, and a bone marrow examination. During treatment patients were interviewed and examined daily. Blood pressure and pulse measurements were done prior to treatment, every 15 minutes for 2 hours after treatment, then every 4 hours during the five day treatment period. On day 1 of therapy, an electrocardiogram was done before drug administration and 1 minute rhythm strips were obtained every 30 minutes for 2 hours. After the first day of treatment, an electrocardiogram was performed daily and when clinically indicated. Holter monitoring of the electrocardiogram during the treatment period was done on at least two patients at each dose level. During treatment hemoglobin, white blood cell and platelet counts were examined daily then twice a week thereafter for three weeks. Urinalysis and blood chemistries were obtained weekly.

Dosage escalation was accomplished in increments of approximately 50% of the preceding dose level. Patients who were unable to complete five days of therapy were observed for three weeks prior to consideration for retreatment. Eight of the ten patients treated with daily doses of 2.3 mg/m² or higher were evaluated with Holter monitoring before treatment and during the first 24 hours of therapy.

Continuous infusion

Toxic limitations of the bolus administration of HH and work by investigators elsewhere (7, 8) led us to change the drug delivery schedule to a five day continuous infusion. The daily dose of HH was diluted in 1,000 ml of 5% dextrose in normal saline administered intravenously over 24 hours. The patient eligibility criteria were the same as for patients given HH as a bolus. Twelve patients were treated with 15 courses of continuous infusion HH (Table 2). Not all patients received a full five day course of treatment. The initial patients were treated with 1.5 mg/m² per day, and because of prior experience elsewhere (7) escalation to 2.3, 3.0, and then 3.5 mg/m²/day followed.

Results

Bolus

The hematologic toxicity seen with bolus administration of HH was distinct from that seen with continuous infusion. Myelosuppression data for the bolus administration are shown in Table 3. Myelosuppression as manifested by leukopenia or thrombocytopenia was not significant for doses as high as 5.0 mg/m²/day for five days.

Cardiovascular toxicity, primarily hypotension, was dose limiting for the bolus administration. Twelve of the eighteen patients treated with this schedule manifested cardiovascular effects during treatment. Six patients demonstrated some degree of hypotension and in two of these patients reduction in systemic blood pressure required cessation of treatment. A 53 year old male with colon carcinoma had a baseline blood pressure of 120/72 and a pulse of 100. He received the first dose of 5.0 mg/m² of HH as a 10 minute bolus. Six hours later his blood pressure was 84/54 with a pulse of 128 per minute. Electrocardiogram revealed mild flattening of T-waves but no other significant findings. No further drug was given and he was treated with intravenous fluids. His blood pressure gradually returned to baseline over the ensuing 48 hours. A 68 year old woman with lung cancer received 5.0 mg/m² which also resulted in delayed hypotension. Her baseline blood pressure was 110/60 with a pulse of 90 per minute. Four hours post-treatment, the pressure was 80/50 with a pulse of 120. She exhibited signs of poor peripheral perfusion with cold extremities and diaphoresis. There was no chest pain or shortness of breath. Treatment included dopamine and norepinephrine without significant effect. Intravenous fluids were continued and the pressure recovered over a period of 18 hours. There was no evidence of cardiac damage by physical examination, electrocardiogram, or serum cardiac enzymes. Four other patients receiving 3.5 mg/m² of HH demonstrated mild hypotension and tachycardia felt to be related to HH. The reduction of blood pressure was 10–20 mm Hg for both systolic and diastolic pressures with concommitant increase in pulse. The reduction of blood pressure usually occurred during the first or second day of therapy and the pressure returned to normal following cessation of therapy. One patient received five days of 5.0 mg/m²/day of bolus HH without tachycardia or hypotension.

To evaluate the role of cardiac function as related to the hypotension, three patients had pre-treat-

Table 3. Hematologic toxicity – Bolus HH

Dose level mg/m²/d × no. days	Number of patients	Number of courses	Median (cells × 1000/cu mm)			
			WBC nadir (range)*	Day (range)	Platelet nadir (range)	Day (range)
0.2 ×5	3	3	3.8 (3.3–7.7)	11 (3–19)	240 (105–258)	18 (18–19)
0.3 ×5	2	2	7.0	—	130	—
0.45×1	1	1	8.6	10	—	—
0.45×2	1	1	7.0	8	472	5
0.45×5	3	3	7.0 (4.2–9.0)	10	300 (203–334)	18 (13–22)
0.7 ×5	2	2	9.4	10	280	13
1.0 ×5	3	3	7.1 (3.9–7.6)	6 (5–18)	280 (200–585)	18 (9–25)
1.5 ×5	3	3	4.7 (2.9–7.7)	9 (5–22)	378 (335–388)	15 (7–16)
2.3 ×2	1	1	—	—	—	—
2.3 ×5	2	2	3.4	16	240	22
3.5 ×2	1	1	2.2	4	107	5
3.5 ×5	5	6	3.8 (3.2–7.1)	8	170 (150–323)	8
5.0 ×1	3	3	6.3 (2.1–6.8)	8 (6–9)	240 (149–330)	10
5.0 ×5	1	1	5.5	8	225	12

* Nadir defined as lowest value after receiving course of therapy.

ment radionuclide ventriculograms followed by repeat studies during drug induced hypotension and tachycardia (Table 4). In none of these patients was there evidence for decreased ventricular function during the periods of hypotension. No hypotensive patient had physical examination or chest radiograph findings suggestive of congestive heart failure.

Seven patients demonstrated sinus tachycardia during treatment. All but one of these patients had simultaneous hypotension. That patient received one dose of 5.0 mg/m² of HH and experienced tachycardia with a resting pulse of 120 per minute without a decrease in the baseline blood pressure of 112/66 mm of Hg. Treatment was discontinued after one dose because of concern for the possibility of hypotension.

Two patients receiving low doses of HH experienced serious cardiac dysrhythmias that may have been drug induced. One woman with a history of mitral valve click-murmur syndrome and metastatic colon carcinoma who received 0.3 mg/m²/d experienced the onset of ventricular bigeminy after day one of treatment. Prior to this course of HH a Holter monitor recording revealed occasional premature ventricular beats but no other dysrhythmia. She was also noted to be mildly hypokalemic during treatment with HH.

A 72 year old man with lung cancer and pleural effusion and a history of right bundle branch block demonstrated the onset of atrial fibrillation within 30 minutes of the second dose of 0.45 mg/m² of HH. Following treatment with digoxin, the cardiac rhythm reverted to normal sinus four hours later. No further HH was given.

Four other patients demonstrated nonspecific changes in electrocardiographic tracings done serially during HH treatment. These changes included increased atrial ectopy in a patient with a history of premature atrial contractions as well as nonspecific ST and T wave changes.

Continuous infusion

In contrast to bolus HH therapy, the administration of HH as a five day continuous infusion caused a different dose limiting toxicity. Prior to the initiation of our continuous infusion trial, other investigators had determined that a dose of 3.75 mg/m²/day for five days given as a continuous infusion caused frequent significant leukopenia and thrombocytopenia (7). Our intention was to explore this dose range to confirm that experience. In our trial, significant myelosuppression was seen at 3.5 mg/m²/day × 5 (Table 5). Six patients were treated with this dose and the median white blood cell count nadir was 2.8 cells × 10^3/mm³ with a range of 1.7 to 11.9 × 10^3 cells/mm³. There was no evidence for preferential toxicity to polymorphonuclear or lymphocytic cell lines. Because of the reproducible WBC suppression and marked thrombocytopenia, escalation of dose was stopped at 3.5 mg/m²/day × 5 days.

Cardiovascular effects that were not dose limiting occurred in patients given HH as a continuous infusion. Six of twelve patients experienced a decrease in blood pressure with concomitant increase in pulse. In three patients the hypotension was significant. During the third hour of the second day of treatment with 2.3 mg/m² a patient experienced a fall in blood pressure from a baseline

Table 4. Left ventricular function after HH 3.5 mg/m² as I.V. Bolus

Patient	Pre HH LVEF*	Post HH LVEF	Time after HH	Heart rate		Blood pressure	
				Pre	Post	Pre	Post
MM	0.59	0.70	3 h	80	110	140/90	130/70
RC	0.71	0.78	4 h	88	120	120/80	100/60
LG	0.71	0.75	4 h	70	120	120/80	120/50

* LVEF = Left Ventricular Ejection Fraction determined from radionuclide ventriculogram.

of 110/80 to 60/40 with a pulse of 120. During this period of hypotension he was noted to have neurologic deficits which led to the diagnosis of brain metastases from an adenocarcinoma of unknown primary. His blood pressure returned to normal with intravenous fluids and discontinuation of HH. A second patient became hypotensive after 16 hours of the first day of 3.5 mg/m² administration of HH. He had received small doses of both diazepam and chloral hydrate within 36 hours of beginning HH treatment. Bleeding from the gastrointestinal tract was also noted during this episode. In a third patient, the blood pressure fell from a baseline of 90/60 to 60/40 after 24 hours of 3.0 mg/m² of HH. The pressure returned to baseline when the HH was discontinued.

Other toxicities

Other toxicities were mild and included an abnormal taste, nausea and vomiting, alopecia, and fever. In the bolus study eight of seventeen patients complained of a metallic or bitter taste within 30 minutes of drug administration. The taste was typically gone by 1 to 2 hours. Patients receiving continuous infusion HH did not experience this taste. Ten of seventeen patients receiving bolus HH and four of twelve in the continuous infusion study had mild nausea and/or vomiting. Symptoms were most pronounced at higher doses but were quite mild at the highest daily dose. Partial alopecia was seen in one patient evaluable for that effect at the 3.5 mg/m²/day × 5 continuous infusion dose. Two patients receiving five days of 2.3 or 3.5 mg/m²/d of HH experienced temperature elevations to 39°C without causes other than HH being identified.

Therapeutic effect

Each patient was evaluated carefully for evidence of antitumor effect following treatment with HH. In the bolus study, five patients had received no prior cytotoxic chemotherapy. Two patients with non small cell lung cancer received 0.45 mg/m² × 2 doses and 0.45 mg/m² × 5 doses without antitumor response. A third patient with a prior history of megestrol acetate for metastatic kidney cancer did not respond to three 5 day courses of HH at dose levels of 0.7, 1.5, and 2.3 mg/m²/day. Two patients with non small cell lung cancer and prior radiotherapy did not have tumor responses to 3.5 mg/m² × 5 and 5.0 mg/m² × 1 respectively.

In the continuous infusion study no response to HH was seen in a previously untreated patient with metastatic colon cancer receiving 3.5 mg/m²/day for five days. In two patients with non small cell carcinoma of the lung previously treated with radiation, HH courses of 3.0 and 3.5 mg/m²/ × 5 respectively did not result in tumor shrinkage.

Table 5. Hematologic toxicity – Continuous Infusion HH

Dose level mg/m²/d × no. days	Number of courses	Median (cells × 1000/cu mm)			
		WBC nadir (range)*	Day (range)	Platelet nadir (range)	Day (range)
1.5 × 5	1	5.2	6	156	6
2.3 × 1	1	—	—	125	15
2.3 × 5	2	4.3	6	124	5
		2.5	11	99	29
3.0 × 1	1	—	—	65	7
3.0 × 4	1	3.5	9	232	5
3.0 × 5	2	4.6	10	204	22
		4.1	20	65	31
3.5 × 5	6	2.8	11	151	11
		(1.7–11.9)	(5–22)	(28–247)	(8–27)

Discussion

In preclinical laboratory testing of the antitumor effects of HH there was a marked schedule dependency. In the clinic we have found that there is likewise a distinct difference in toxicity depending on the schedule of administration. Bolus administration led to a maximum tolerated dose of 3.5 mg/m²/day with the dose limiting toxicity being hypotension. For a five day continuous infusion significant myelosuppression occurred with a dose of 3.5 mg/m²/day and cardiovascular toxicity, though seen, was not dose limiting.

The fall in blood pressure seen with bolus HH occurred 4 or more hours after drug administration, did not quickly reverse with fluid administration or, in some cases, pressor therapy, and was clinically a result of peripheral vasodilation rather than myocardial dysfunction. In fact, in the patients studied with radionuclide ventriculograms, left ventricular contactility increased during periods of HH induced tachycardia and decreased blood pressure.

We were unable to predict which patients would experience hypotension, however, in retrospect there may be certain predisposing factors including the use of central nervous system active agents such as sedatives or narcotics. Though clinically the hypotension is related to peripheral vascular vasodilation as manifested by good myocardial performance and reflex tachycardia, the precise mechanism is not clear. Consistent findings included a delay of at least several hours between drug administration and hypotension, a return to baseline within 48 hours after the onset of hypotension if further drug is withheld, and lack of residual toxicity. The one patient who received five days of 5.0 mg/m²/day HH had no hypotension but had previously been treated with 4 courses of lower doses of bolus HH during the preceding 6 months, also without hypotension. His ability to receive this amount of drug without hypotension could perhaps be attributed to his young age (32 years) or perhaps the development of a "tolerance" to the hypotensive effect of the drug.

Chinese investigators have reported 'cardiovascular toxicity' in trials of HH and the related harringtonines. The cardiovascular effects are not detailed, however the recommended mode of delivery is by 'slow intravenous drip'. It is also mentioned that a small initial dose with gradual dosage increase is better tolerated.

Of the four patients receiving a bolus HH dose of 5.0 mg/m², two had significant hypotension requiring cessation of HH treatment. The dose of 3.5 mg/m²/day × 5 was tolerable with 4 of 6 courses (in five patients) resulting in mild asymptomatic reductions of blood pressure of less than 15 mm of Hg systolic and diastolic. It must be noted that this dose of HH resulted in a median white blood cell and platelet nadir of 3.8 and 170 × 10³ respectively. Because of the modest myelosuppression and the significant risk associated with doses higher than 3.5 mg/m² we do not recommend Phase II trials of HH using a bolus schedule unless further studies determine an understanding of the hypotensive mechanism and a means for prevention of serious hypotension.

Continuous infusion HH, however, was well tolerated and caused significant myelosuppression in 5 of 6 courses of 3.5 mg/m²/day × 5. In two of these patients, the nadir platelet count was less than 50,000/mm³, and because of this degree of thrombocytopenia, there was no further dose escalation.

The Chinese scientists used several schedules to simultaneously evaluate the toxicity and therapeutic effectiveness of a mixture of harringtonine and homoharringtonine in patients with a variety of acute leukemias. Patients were treated with intramuscular drug at a dose of 2 mg/day for 9–10 days, or 4 mg/day as a slow intravenous drip for 23–86 days. The other treatment schedule utilized the H + HH mixture intravenously given over 15 minutes at a dose of 5–6 mg/day for 4 to 6 days (2). A later report tested a dose of 0.2–0.3 mg/kg/day for 5–7 days given as a slow intravenous drip (3). Since therapeutic effect, including 'remissions', was seen with all of the above schedules, it is necessary to evaluate the effectiveness of the treatment in light of current approaches to the therapy of acute leukemia in the United States. Standard treatment is directed at rapid ablation of the leukemia cell population so as to return the bone marrow to a normal condition as soon as possible. However,